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# Sleep Apnea and the Kidney

## Is Sleep Apnea a Risk Factor for Chronic Kidney Disease?

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The prevalence of chronic kidney disease (CKD) is increasing, which presents challenges for both patients and health-care budgets. Although this phenomenon has been attributed to the growth in diabetes, hypertension, and obesity, sleep apnea and nocturnal hypoxemia may also contribute to the pathogenesis of CKD and its progression to kidney failure. Two pathophysiologic mechanisms responsible for CKD are glomerular hyperfiltration and chronic intrarenal hypoxia, resulting in tubulointerstitial injury, the final common pathway to end-stage kidney disease (ESKD). Multiple descriptive studies have demonstrated an association between CKD and sleep apnea. Although sleep apnea is common in patients with CKD and associated with significant nocturnal hypoxemia, it is often relatively free of sleep-related symptoms, making it difficult to detect without objective nocturnal monitoring. Nevertheless, sleep apnea and nocturnal hypoxemia have been associated with loss of kidney function and kidney injury, suggesting that they contribute to the pathogenesis of continued deterioration in kidney function. There are several pathways through which sleep apnea may achieve this, including a direct effect of intrarenal hypoxia and activation of the systemic and renal renin-angiotensin system. Further research is required to better understand these relationships and determine whether specific interventions in patients with sleep apnea have an impact on clinical outcomes, such as reducing the prevalence of CKD and delaying its progression to ESKD.

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**ABBREVIATIONS:** AHI = apnea-hypopnea index; AngII = angiotensin II; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; FF = filtration fraction; GFR = glomerular filtration rate; PSG = polysomnography; RAS = renin-angiotensin system; RDI = respiratory disturbance index; RPF = renal plasma flow; PSQI = Pittsburg Sleep Quality Index; $Sao_2$ = arterial oxygen saturation

It is well recognized that end-stage kidney disease (ESKD) is associated with an increased prevalence and severity of sleep apnea,[1-4] the pathophysiology of which is related to both destabilization of central ventilatory control and upper airway occlusion during sleep.[5-7] Sleep apnea is an important comorbidity in patients with ESKD and contributes to the pathogenesis of excessive daytime sleepiness[8] and has the potential to increase cardiovascular morbidity and mortality.[9] More recently, the potential impact of OSA on the development of chronic kidney disease (CKD) has

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received increasing attention in the medical literature. These findings raise the possibility that a bidirectional relationship exists between sleep apnea and kidney disease.

The global prevalence of CKD has increased significantly over the past decade,[10-12] particularly in the older population. More than 10% of adults have CKD,[13,14] and this figure rises to 20% in those aged > 60 years and to 35% in those aged > 70 years.[10] Although this phenomenon has been largely attributed to the increasing prevalence of diabetes, hypertension, and obesity,[12,15,16] these chronic medical disorders do not fully explain the growing prevalence of CKD.[10] Undiagnosed sleep apnea is common,[17] and its prevalence has increased dramatically in the past 2 decades.[18] Sleep apnea may also contribute to the progression of kidney disease either directly through the effects of hypoxia on the kidney[19,20] or indirectly by increasing oxidative stress and endothelial dysfunction, inflammatory cytokine levels, sympathetic nervous system activity, and systemic BP, all of which have been proposed to reduce kidney function.[21-23] Because reduced kidney function increases the risk of cardiovascular morbidity and death[24] and progression of CKD to renal replacement therapy carries an enormous economic burden,[10,13,25] a better understanding of the potential role of sleep apnea in facilitating these changes is important to both clinicians and health policymakers. This article reviews the pathogenesis of kidney disease, summarizes the data on the prevalence of sleep apnea in the CKD population and its potential impact on kidney function, and outlines pathophysiologic mechanisms through which sleep apnea may damage the kidney.

## Pathogenesis of Kidney Disease

Conceptually, the kidney can be considered to consist of two functionally distinct but anatomically connected areas, namely the glomerulus, which is found predominantly in the cortex of the kidney, and the renal tubule, which is located predominantly in the renal medulla (Fig 1[26]). Blood flows from the interlobular artery through the afferent arteriole to reach the capillary network within each glomerulus and leaves through the efferent arteriole to pass through the peritubular capillaries before exiting the kidney through the interlobular vein. Urine is produced by filtration at the glomerulus and reabsorption at the kidney tubule and is transported through the collecting system to the ureter.

CKD is believed to start with an initial injury arising from a variety of sources.[12,27] Once the injury has reached a critical threshold, additional physiologic processes within the kidney, which are largely independent of the initial insult, drive the progression to kidney failure.[12,19] These mechanisms occur at the glomerulus (glomerular hyperfiltration theory)[25] and the renal tubule (chronic hypoxia hypothesis).[19,20,27] The glomerular hyperfiltration theory was proposed by Brenner et al[28] in 1982, who suggested that a critical loss of nephrons from the initial injury results in a compensatory increase in activity in the remaining nephrons to maintain adequate clearance and glomerular filtration rate (GFR). Glomerular hyperfiltration is achieved largely by vasodilation of the afferent arteriole, which increases renal plasma flow and glomerular capillary pressure. Although this maintains GFR in the short term, it damages the glomerulus in the long term, resulting in the development of glomerulosclerosis. Furthermore, glomerular capillary hypertension impairs the sieving function of the glomerulus, resulting in protein overload that stimulates inflammation and fibrosis in the interstitium of the kidney.[29]

Although glomerular hypertension remains an important mechanism in the pathogenesis of CKD, damage to the kidney tubule and interstitium that surrounds it (tubulointerstitial injury) correlate better with the degree of kidney dysfunction. In fact, it has been proposed that tubulointerstitial injury, partly due to chronic hypoxia, is the final common pathway to ESKD.[27] Although the kidney receives 20% of the total cardiac output, the supply of oxygen to the renal medulla, which receives only 10% of total renal blood flow,[30] is compromised by both anatomic and physiologic factors. Anatomically, the renal medulla is relatively remote from the blood vessels that supply oxygen to the kidney. Physiologically, the countercurrent mechanism through which the renal tubule operates effectively provides an arteriovenous shunt for oxygen through the vasa recta. This compromised oxygen supply is further aggravated by an intermittently high oxygen consumption promoted by normal renal physiologic activities, such as active sodium reabsorption. The imbalance between limited oxygen supply and heavy demand in the renal medulla makes the kidney vulnerable to hypoxic injury.[31] Intrarenal hypoxia has been demonstrated in humans with CKD[32] (Fig 2), and renal tissue hypoxia in experimental animal models causes proteinuria independently of other hemodynamic or biochemical changes.[33] It has been proposed that the renal parenchyma can respond to hypoxia through both protective pathways mediated by hypoxia-inducible factor and potentially harmful